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The Role of Compensation in Nicotine Reduction

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Abstract

The available research on switching from normal nicotine to very low nicotine content cigarettes shows minimal evidence of compensatory smoking. Mathematical estimations suggest that substantial compensation after switching to very low nicotine cigarettes would be impossible. It is likely that smokers who are unable to tolerate the extent of proposed nicotine reduction would switch to other sources of nicotine, rather than try to compensate by smoking more very low nicotine content cigarettes more intensely.

Introduction

As the Food and Drug Administration (FDA) considers implementing a reduced nicotine standard, it is important to consider how smokers' behavior may change in response to very low nicotine content (VLNC) cigarettes. When faced with a potential reduction of nicotine availability, smokers may try to adjust their smoking behavior (either by smoking their cigarettes more intensely, or by increasing the number that they smoke per day) to maintain desired levels of nicotine intake. This is called compensation. In addicted cigarette smokers, there appears to be an optimal level of daily intake of nicotine that provides the desired rewards from smoking, including avoidance of nicotine withdrawal symptoms.[1] Thus, smokers tend to take in a similar amount of nicotine from their cigarettes day after day. Compensation is seen when smokers switch from normal nicotine to low nicotine yield commercial cigarettes (ie, light cigarettes) and when the number of cigarettes one can smoke is limited.

How Does Compensation Occur?

Compensation for reduced nicotine yield cigarettes is relatively easy because the nicotine content of the tobacco filler (generally between 10 and 15 mg) is similar for normal and low nicotine yield commercial cigarettes. They are considered low yield based on smoking machine testing, which consists of taking a standard number of puffs of fixed duration and at fixed intervals until the cigarettes burn to the filter overwrap. Low-yield commercial cigarettes are engineered to burn more quickly and/or to have greater ventilation via changes in the cigarette paper and/or ventilation holes in the filter, compared with normal nicotine yield cigarettes.[2] The smoker can easily compensate by inhaling more deeply, taking more frequent puffs, blocking ventilation holes with fingers or mouth, and/or smoking more cigarettes per day (CPD). Compensation occurs with minimal effort and often without the smoker being aware of the change in behavior.

Compensation for smoking fewer cigarettes per day occurs through similar changes in puff topography. Assuming a cigarette contains 10–15 mg of nicotine, and the smoker takes in a systemic dose of 1 mg nicotine (both typical values), then the bioavailability is only about 6%–10%. A smoker can, by puffing more frequently and more intensively increase bioavailability 3–4 fold, such that a dose of 3–4 mg nicotine can be obtained per cigarette, effectively maintaining nicotine exposure even when the number of cigarettes smoked is reduced.[3]

Is It Possible to Engage in Compensatory Smoking Behavior When Switching to VLNC Cigarettes?

Effectively compensating to maintain nicotine exposure is virtually impossible when switching to cigarettes with minimally addictive nicotine content (e.g., VLNC). The amount of nicotine needed to make cigarettes minimally addictive appears to be 0.4 to 0.5 mg nicotine per gram of tobacco in the tobacco rod (this may be different for other combusted products such as cigars).[4] This represents a reduction of nicotine content of 95% or more compared with currently available commercial cigarettes. Assuming the tobacco in a cigarette weighs 0.7 gm, a cigarette containing 0.4 mg/gm tobacco would contain 0.28 mg nicotine. Assuming the usual level of bioavailability, the systemic dose per cigarette would be around 0.025 mg. Assuming the most intensive compensatory inhalation of a 4-fold increase, the maximal systemic dose per cigarette would be about 0.1 mg. These doses are in contrast to the 1 mg or more taken systemically from a currently marketed cigarette. Assuming that a 10 CPD smoker is trying to maintain an intake of 10 mg nicotine per day, and assuming the most intensive compensation, it would require that the smoker smoke 100 CPD to achieve full compensation. It is likely impossible that a person could smoke 100 CPD at maximal intensity, so full compensation would be impossible. More likely, the smoker would try to smoke more intensively and smoke more cigarettes per day at first, find compensation impossible, and give up. As nicotine intake falls, one would predict that the level of nicotine dependence would likewise decline, and eventually the smoker would find the cigarette unrewarding and quit. Alternatively, the smoker may seek other available forms of nicotine to satisfy their need for nicotine.

Is There Evidence of Compensation in VLNC Clinical Trials?

A number of clinical trials have assessed compensation across a variety of measures when smokers are switched from Normal Nicotine Content (NNC) to VLNC cigarettes and found minimal compensatory smoking behavior. Compensation has been assessed by measuring CPD, nicotine intake (blood levels of nicotine and cotinine or urine total nicotine equivalents), by exposure to tobacco combustion toxicant biomarkers (carbon monoxide, polycyclic aromatic hydrocarbons) and tobacco specific nitrosamines (NNAL), and by smoking topography. Trials have been done with single reduced nicotine content cigarettes, with switching from periods of 4 weeks to 1 year, and with gradual and immediate reduction of nicotine content levels.[4–8] In a study of smokers smoking a single cigarette of different nicotine content on separate days, the intake of nicotine based on area under the plasma nicotine concentration time curve was highly correlated with the nicotine content of the cigarette.[9] Compensation when smoking the lowest nicotine content cigarette (0.6 mg nicotine per cigarette) compared with a 10 mg nicotine content cigarette was 33% with no difference in carbon monoxide exposure. Furthermore, a study by MacQueen et al. indicated that increases in total puff volume were confined to the first few cigarettes and quickly returned to control levels.[10]

Several studies have looked at switching smokers to VLNC for weeks or up to 1 year.[4–8,10] These studies were quite consistent, showing a reduction of plasma cotinine or urine total nicotine equivalent levels of about 60% to 70% (data synthesized by Hatsukami et al. 2015).[11] Overall, at the end of the study period, there was a significant decrease in CPD, although with gradual reduction there was a slight increase in CPD compared with baseline at medium nicotine content level, then a decline in CPD as nicotine content was further decreased. Expired carbon monoxide and polycyclic aromatic hydrocarbon exposure was unchanged by condition, indicating no harmful over-smoking. Urine NNAL levels decreased in all reduced nicotine content cigarettes studies compared with baseline, but this does not inform compensation because the NNK levels in reduced nicotine content cigarettes are lower than currently marketed commercial cigarettes. One study found that total puff volume when smoking a single cigarette was significantly lower when smoking 0.4 mg/gm tobacco cigarettes compared with baseline.[4] The observation that with gradual reduction there was evidence consistent with some compensatory smoking with more CPD when cigarettes contained medium levels of nicotine supports the idea that nicotine levels need to be reduced to lower levels at which compensatory smoking is not feasible.

Are There Limitations in the Interpretation of Clinical Trials That Switch Smokers to VLNC Cigarettes?

The main limitation in interpreting the switching studies with respect to compensation is the noncompliance with research VLNCs. Based on biochemical assessments, noncompliance with study cigarettes is as high as 80%.[12] Noncompliance is unavoidable in real world studies because usual brand cigarettes are readily available. Compliance is partial such that, as described above, nicotine intake decreases to 30%–40% of baseline, but this decline is less than expected based on the extent of nicotine reduction. Smokers typically smoked a few NNC cigarettes per day. Presumably, these cigarettes provide some of the nicotine that the addicted smoker cannot get from the VLNC. We do not yet know the extent of compensatory smoking behavior that would occur if higher nicotine content cigarettes were unavailable, as would be the case if all cigarettes were mandated to be VLNC. However, when confined to a residential research facility for 11 days, participants smoked fewer cigarettes per day and had lower exhaled carbon monoxide when randomized to very low nicotine versus control cigarettes.[13]

Another potential limitation is that experimental studies include subjects who have volunteered to participate. It is possible that more highly addicted smokers who might have trouble with nicotine reduction would not have volunteered to participate, or would have dropped out of studies.

Conclusions

The available research on switching from NNCs to VLNCs shows minimal evidence of compensatory smoking such that smokers do not smoke more cigarettes per day and are not exposed to higher levels of tobacco combustion toxicants. Furthermore, mathematical estimations based on the nicotine availability in VLNCs compared with NNC cigarettes with consideration of potential increases in bioavailability that could occur with intensive smoking suggest that substantial compensation would be impossible. It is much more likely that smokers who are unable to tolerate the extent of proposed nicotine reduction would switch to other sources of nicotine, rather than try to compensate by smoking more VLNC cigarettes more intensively.

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Declaration of Interests

Dr. Benowitz is a consultant to Pfizer and Achieve Life Sciences, companies that market or are developing smoking cessation medications, and has been a paid expert witness in litigation against tobacco companies. The other authors have no conflicts to disclose.

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